Public Workshop - Patient and Medical Professional Perspectives on the Return of Genetic Test Results

March 2, 2016

Center for Devices and Radiological Health
CDRH

Docket No. FDA-2015-N-4809

#precisionFDA
#precisionmedicine

Housekeeping

- Please set computers, cell phones, and Blackberries on silent mode, and answer all calls in the hallway
- Webcast at https://collaboration.fda.gov/genetictest0316/
- Wi-Fi can be accessed in the Great Room area using *guestaccess*
- Links to the meeting transcript and the archived webcast will be posted to the workshop registration webpage approximately 6-8 weeks after the meeting
- Food and beverages will be available for purchase by workshop participants at the Sodexo kiosk in the registration lobby.

Participation in a public meeting by an individual or an organization does not imply any endorsement by the Food and Drug Administration.

The FDA encourages and supports the exchange and dissemination of information on research and development of health care products, regulatory processes, emerging technologies, and information management.

The FDA strives to provide a neutral forum for education and discussion opportunities concerning the latest technologies and processes. Preservation of the neutrality of this forum, fostering collaborative efforts, is essential to maintaining the impartiality of the federal government.

Introduction

Bruce Kuhlik, JD
Senior Advisor to the Commissioner
Food and Drug Administration

Introduction

Jo Handelsman, PhD

Associate Director for Science in the Office of Science and Technology Policy

White House

Introduction

Kathy Hudson, PhD
Deputy Director for Science, Outreach and Policy
National Institutes of Health

The Precision Medicine Initiative® Cohort Program

Kathy Hudson, PhD
NIH Deputy Director for Science, Outreach, and Policy

Follow me @KathyHudsonNIH

"And that's why we're here today. Because something called precision medicine … gives us one of the greatest opportunities for new medical breakthroughs that we have ever seen."

President Barack Obama

January 30, 2015

“It requires, first of all, us understanding who owns the data," And I would like to think that if somebody does a test on me or my genes, that that's mine..”

President Barack Obama

February 25, 2016

Health | Nation | Nation & World

Who owns your genetic data? Obama says you do

Originally published February 25, 2016 at 9:54 pm | *Updated February 25, 2016 at 9:57 pm*

Many researchers and the universities and medical centers that back them regard genetic material and the results from tests they conduct on it as their intellectual property and are reluctant to share it

By JULIE HIRSCHFELD DAVIS
The New York Times

Share story

Share

Email

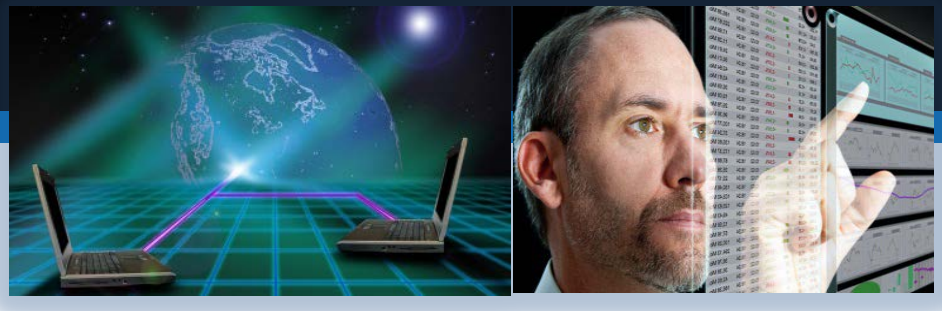
Tweet

WASHINGTON — President Obama on Thursday waded into the complex and high-stakes debate over whether patients own their genetic information, saying he believes his tissues and any discoveries that stem from his DNA belong to him.

"I would like to think that if somebody does a test on me or my genes, that that's mine, but that's not always how we define these issues," Obama said during a White House forum on a major biomedical research initiative he began last year.

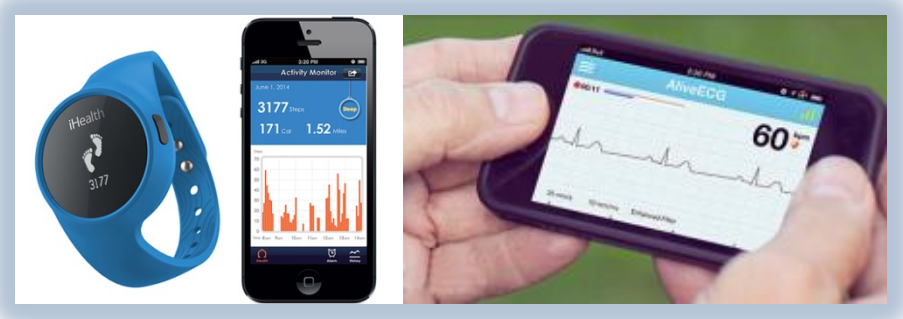
Assembling the PMI Cohort

- **One million or more** U.S. volunteers
  - Broadly reflect the diversity of America (including family members of all ages, health statuses, areas)
  - Strong focus on underrepresented groups
- **Longitudinal cohort**, with continuing interactions, recontactable for secondary studies
- Two methods of **enrollment**
  - Direct volunteers
  - Healthcare provider organizations (incl. FQHCs)
- Substantial **participant engagement** in development, implementation, governance



Data Science

EHRs



Technologies

Genomics

Engaged Participants

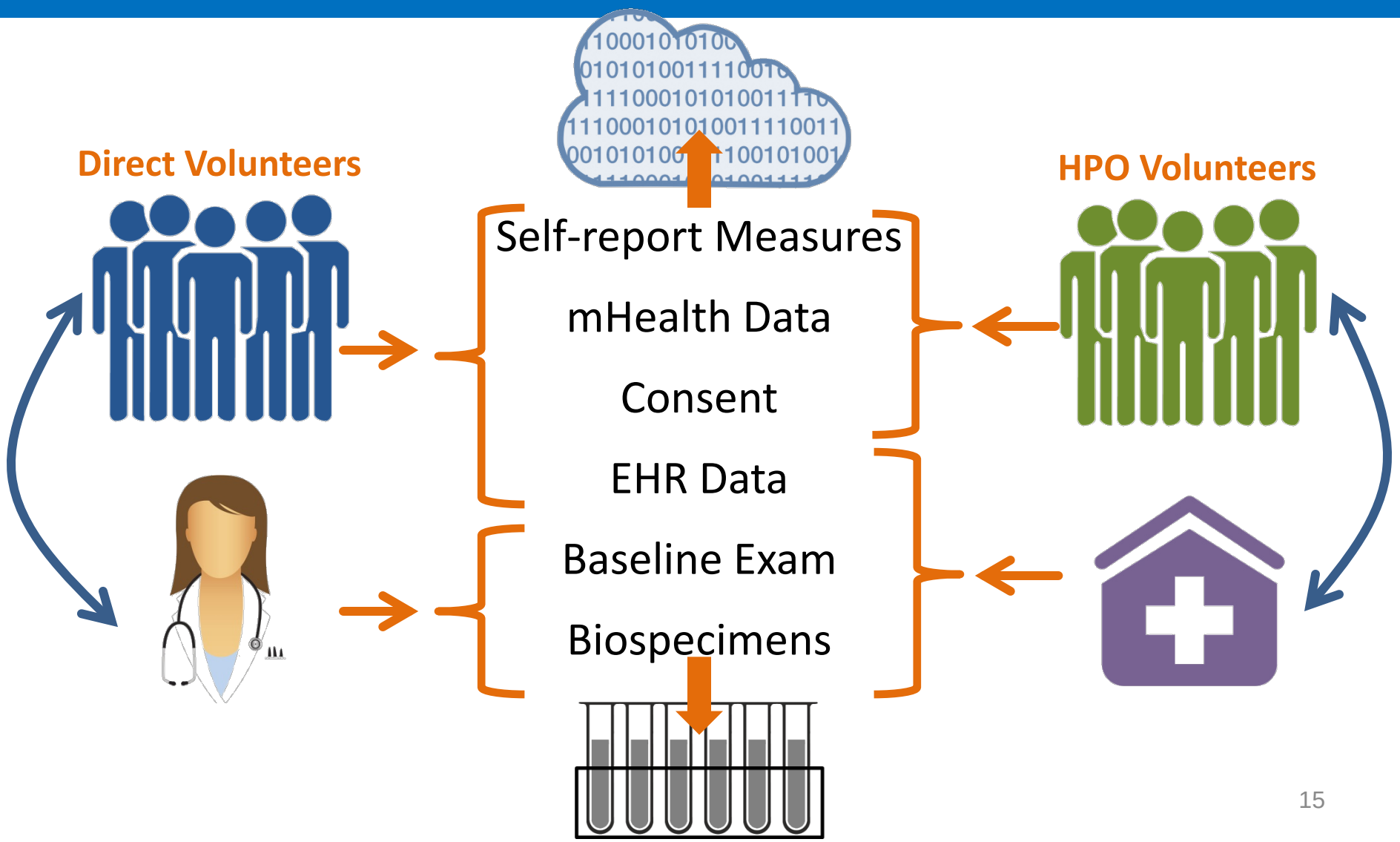
PMI Core Values

1. Participation is **open** to interested individuals
2. Representing the **rich diversity** of America is essential
3. Participants are **partners** in all phases of the cohort program
4. Participants have **access to study information** and data about themselves
5. Data can be **accessed broadly** for research purposes
6. Adherence to the PMI **privacy principles** and forth-coming security framework
7. PMI is a **catalyst** for progressive research programs and policies

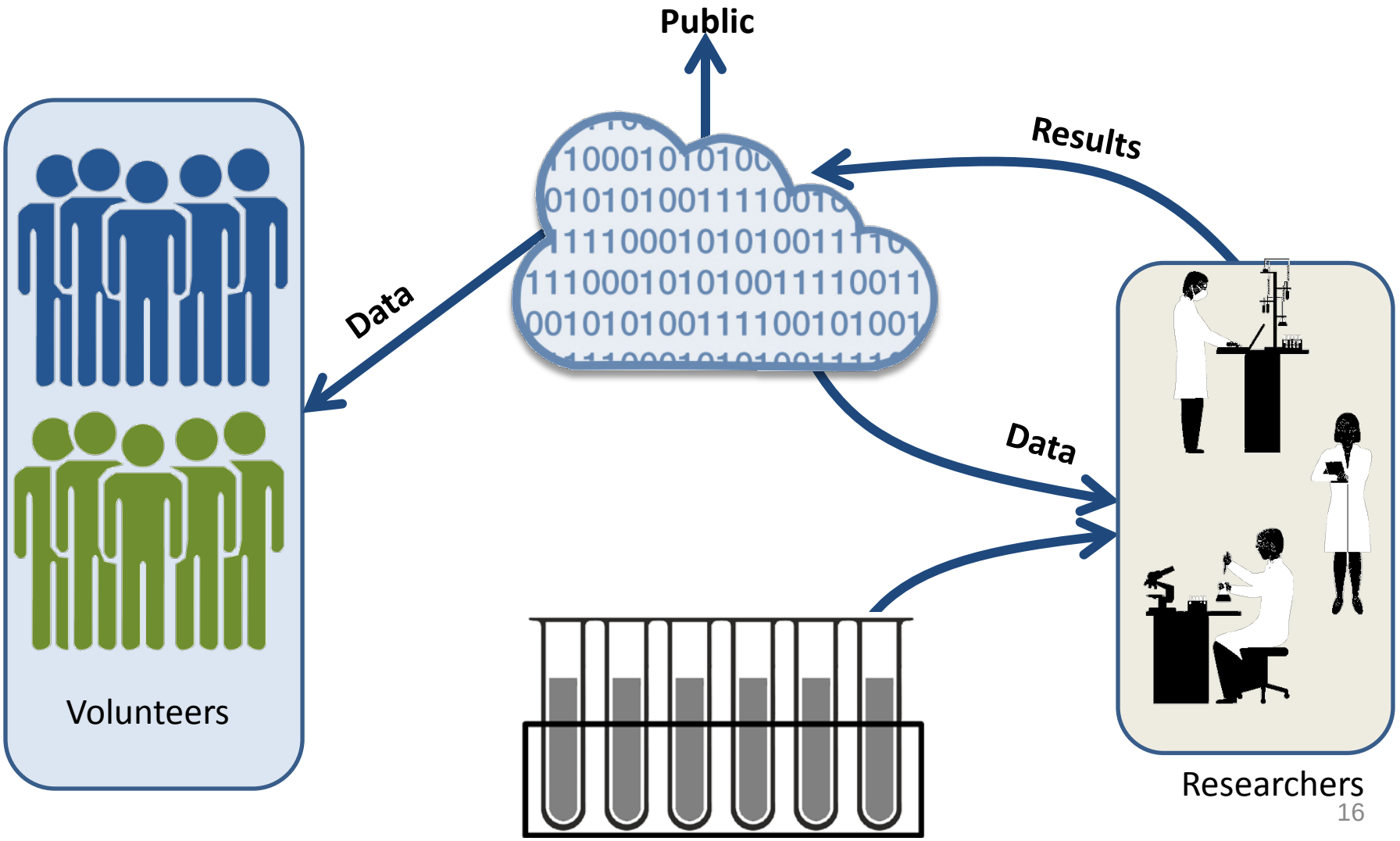
FNIH Survey of public opinion on a large US cohort study

- 79% agree cohort probably/definitely should be done
- 54% would probably/definitely participate in the cohort
- What motivates participation?
  - 82% interested in receiving results of study
  - 62% wish to help advance health research
- 71% said participants should be partners with researchers

Information Flow In



Information Flow Out



Return of Results and Data

- Participants may receive, depending on their preferences:
  - Individual data
  - Individual health information
  - Ongoing study updates
  - Aggregated results

Today's Questions

- What are considerations for providing research data to participants and patients?
- Why do we think participants will not use information about their health wisely?

What is unique about genetic data?

We trust patients to interpret complex labeling, family history, other biological measures, why not genetic information?

Would you want to know if researchers found that you…

have a genetic risk factor for a treatable disease like severe asthma? 87%

were at increased risk for a treatable disease like severe asthma? 89%

---

have a genetic risk factor for an untreatable disease like Alzheimer's? 81%

were at increased risk for an untreatable disease like Alzheimer's? 83%

FNIH/PMI 2015 n=2061

Would you want to know if researchers found that you…

have a genetic risk factor for having a bad reaction to certain types of medicine? 89%

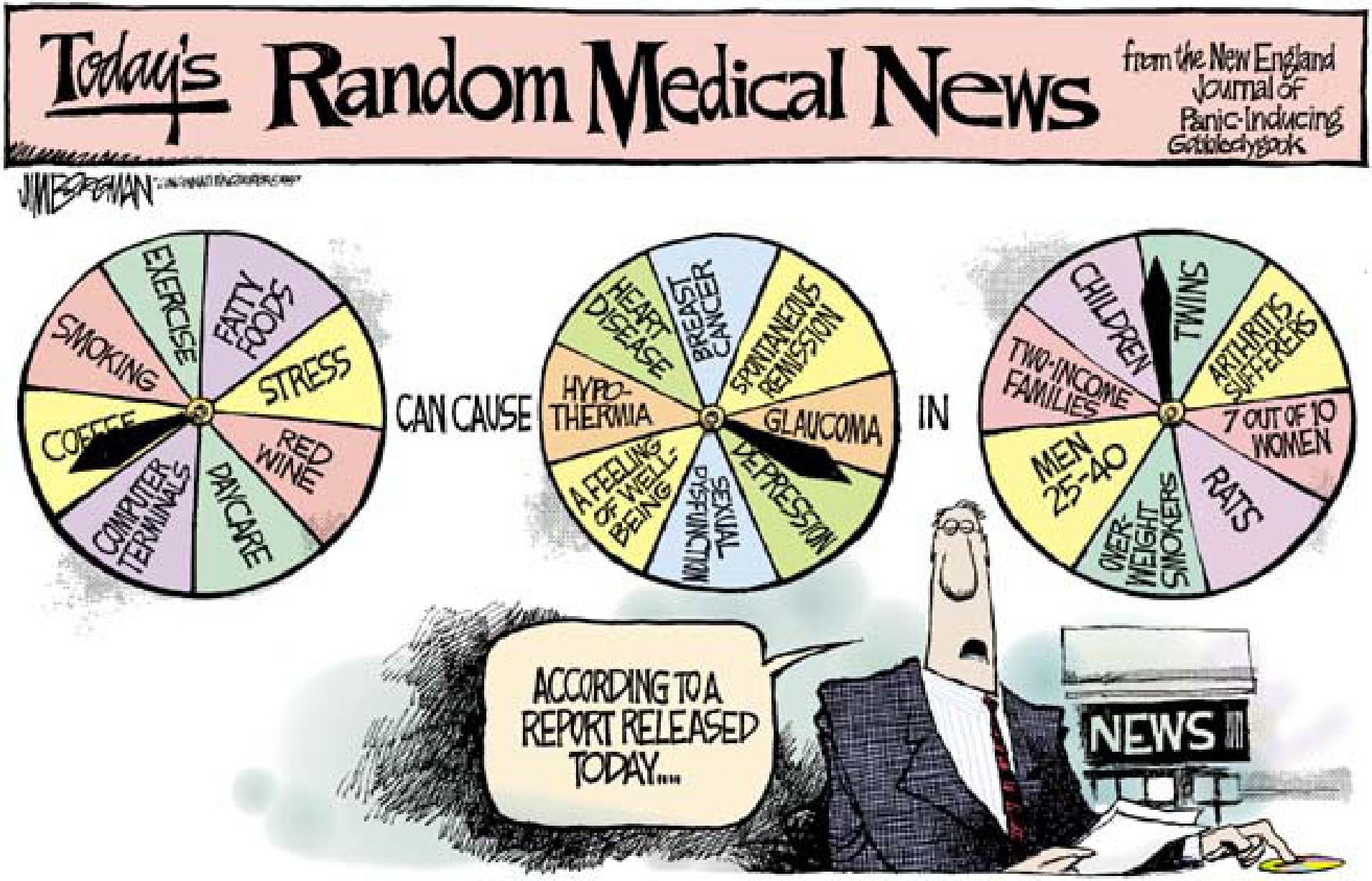
were at increased risk for having a bad reaction to certain types of medicine? 90%

---

have a genetic risk factor for something unusual that researchers do not really understand? 79%

were at increased risk for something unusual that researchers do not really understand? 79%

FNIH/PMI 2015 n=2061


Today's Random Medical News
from the New England Journal of Panic-Inducing Gobbledygook
JIM BORGMAN
SMOKING
EXERCISE
FATTY FOODS
STRESS
RED WINE
DAYCARE
COMPUTER TERMINALS
COFFEE
CAN CAUSE
HEART DISEASE
BREAST CANCER
SPONTANEOUS REMISSION
HYPO-THERMIA
GLAUCOMA
A FEELING OF WELL-BEING
SEXUAL DYSFUNCTION
DEPRESSION
IN
CHILDREN
TWINS
ARTHRITIS SUFFERERS
TWO-INCOME FAMILIES
7 OUT OF 10 WOMEN
MEN 25-40
OVER-WEIGHT SMOKERS
RATS
ACCORDING TO A REPORT RELEASED TODAY...
NEWS

Thank you!

Introduction

Liz Mansfield PhD
Deputy Office Director for Personalized Medicine
Food and Drug Administration

Panel 1: Well Patient/Predictive Tests

- Moderator: Cara Tenenbaum, JD, CDRH

- Sara Weir, National Down Syndrome Society
- Tracy Trotter, MD, San Ramon Valley Internal Medicine
- Margot Savoy, MD, MPH, FAAFP, Family Medicine Center-Christiana
- Ellen Matloff, MS, CGC, My Gene Counsel
- Steven J. Ralston, MD, Beth Israel Deaconess Medical Center

#precisionFDA
#precisionmedicine

Case Study

John is a 30 year old Latino with a high school education. He is concerned that his grandfather was recently diagnosed with Alzheimer's disease at age 85 and read about a new test that can tell him if he's likely to develop the condition.

A: You are John. Consider the following:

- You have a mutation that, based on published data, gives you a 90% chance of developing early onset Alzheimer's.
- You have a mutation that, based on published data, gives you a 35% chance of developing Alzheimer's.
- You have a mutation that has contradictory evidence suggesting you are anywhere between 3 and 30% more likely to develop Alzheimer's than average.
- There is limited evidence regarding the clinical effect of this mutation
- You do not have any mutations that we know are connected to developing Alzheimer's disease.

BREAK

Panel 2: Acute Disease Tests

- Moderator: Laura Koontz, PhD, CDRH

- Lisa Schlager, Facing Our Risk of Cancer Empowered
- Annie Kennedy, Parent Project Muscular Dystrophy
- Girish Putcha, MD, PhD, Palmetto GBA
- Barbara Biesecker, PhD, NHGRI
- Carolyn Hendricks, MD, US Oncology

#precisionFDA
#precisionmedicine

Case Study

Carole is a 63 year old college educated woman who has a family history of cancer but no known pattern of specific cancers. Her family is of Middle Eastern and Asian heritage. She is diagnosed with lung cancer and has her tumor's genome sequenced.

A: You are Carole. What information would you like? How would you like it presented? What would you do with it? Consider the following:

- Your lung cancer has a mutation for an FDA-approved companion therapy for lung cancers
- Your lung cancer has a mutation for a an FDA-approved companion therapy for breast cancers
- Your lung cancer has a mutation that may be connected to higher response rates in prostate cancers
- Your lung cancer has multiple mutations that may suggest different courses of therapies

B: You are Carole's oncologist. What information would you like? How would you like it presented? What would you do with it? Consider the following:

- Her lung cancer has a mutation for an FDA-approved companion therapy for lung cancers
- Her lung cancer has a mutation for a an FDA-approved companion therapy for breast cancers
- Her lung cancer has a mutation that may be connected to higher response rates in prostate cancers

LUNCH

Panel 3: Chronic Disease Tests

- Moderator: Katherine Donigan, PhD, CDRH

- Francis J. McMahon, MD, National Institute of Mental Health
- Anna McCollister-Slipp, Scripps Translational Science Institute
- Kiran Musunuru, MD, PhD, MPH, Harvard University
- Amy Sturm, MS, CGC, The Ohio State University, National Society of Genetic Counselors
- Allen Doederlein, Depression and Bipolar Support Alliance

#precisionFDA
#precisionmedicine

Case Study

Doug is 22 year old Caucasian with a history of depression and schizophrenia that are moderately well-controlled with drugs and therapy. His aunt tells him about a test his doctor can order to help him find the perfect drugs for his conditions by sending in a simple cheek swab.

A: You are Doug. What information would you like? How would you like it presented? What would you do with it? Consider the following:

- The data guiding the treatment recommendations is not well-developed
- The treatment recommendations are provided as strongly recommended for a number of different options
- The treatment recommendations from the test conflict with your current regimen

B: You are Doug's psychiatrist. What information would you like? How would you like it presented? What would you do with it? Consider the following:

- The data guiding the treatment recommendations is not well-developed
- The treatment recommendations are provided as strongly recommended for a number of different options
- The treatment recommendations from the test conflict with his current regimen

BREAK

PUBLIC COMMENT

Kathy Hibbs

23andMe

Lisa Schlager

FORCE: Facing Our Risk of Cancer Empowered

James Gelfand

March of Dimes

Girish Putcha

Palmetto GBA/MolDX

MolDX®

PALMETTO GBA®
A CELERIAN GROUP COMPANY

Public Workshop
Perspectives on Return of Genetic Test Results
02 March 2016

Girish Putcha, MD, PhD
Director of Laboratory Science

Please note that the opinions expressed herein are my own.

Tissue Sequencing-based Somatic Oncology Tests

- Claims of >99% “sensitivity” and/or “specificity” when analytic performance varies meaningfully with alteration type, variant allele frequency (VAF), etc
  - Single nucleotide variants (SNVs) at VAF > 10%: PPA ≥ 99%
  - Amplifications at 20-30% tumor nuclei: PPA ≥ 60%
- Essentially unregulated marketing blurs important differences among panels
  - Testing an NSCLC patient for ALK SNVs and indels (i.e., a “hotspot” panel) clearly not as useful as one that tests for ALK rearrangements
- Often vague, inconsistent and generous definitions of “actionable”:
  - FDA approved drug targeting a gene alteration in patient’s tumor type (or in another tumor type)
  - Clinical trial with drug targeting a gene alteration in patient’s tumor (or in another tumor type)
- “More is better”: When even NCCN (with varying levels of evidence) recommends only 10 somatic targets for 6 different tumor types, what’s the clinical utility of testing tens or even hundreds in every tumor?
- Safety and efficacy of drug therapy directed by non-companion diagnostic tests is essentially unknown.

Please note that the opinions expressed herein are my own.

Pharmacogenomic Tests

- What is “actionable”?
  - Do test results actually change patient management (e.g., drug selection, dose, and/or schedule)?
  - Do such changes actually improve net health outcomes (e.g., efficacy, safety, etc)?
- FDA labels rarely require such testing for drug selection, dose, and/or schedule.
- Other guidelines (e.g., CPIC) generally do not require such testing for drug selection, dose, and/or schedule, but instead provide guidance on how to interpret test results when available.

Please note that the opinions expressed herein are my own.

Non-invasive Prenatal Screening

- Initial clinical validation studies generally
  - Not in intended use populations (i.e., contrived case control cohorts), even for “high risk” let alone “average risk”
  - Excluded “hardest” admittedly infrequent cases (e.g., partial aneuploidies, balanced translocations, mosaics, etc)
- Subsequent clinical studies generally
  - Compared to a suboptimal test (i.e., not “best practice”)
  - Had some (potentially significant) biases in design (e.g., timing of sampling)
- Performance can vary meaningfully with alteration type
  - Analytical PPV (i.e., not adjusted for prevalence) for T21 = 92 % (88-95%); for SCA = 35 (23-49%); for microdeletion syndromes 11 (1-35%)[1]
- Health economic questions aside, appropriate clinical use may change when these limitations are considered.

Please note that the opinions expressed herein are my own.

[1] Meck et al., 2015; Wang et al., 2015

Themes & Comments

- Many (if not all) are LDTs, now offered nationally and even internationally, at least some from CAP-accredited and/or NY-permitted clinical laboratories
- True innovation in healthcare improves patient care and/or wellness (e.g., efficacy, safety, convenience, compliance, etc)
  - Inherently comparative to some standard of care
    - "Real world" or "best practices" (e.g., guideline-based)?
    - Should tests substitute for adherence to guidelines?
  - Cool science + aggressive marketing ≠ good medicine
- Regulatory (and reimbursement) policies can (and ideally should) facilitate such innovation.

Please note that the opinions expressed herein are my own.

Final Thoughts

- Whatever it's ultimate role in regulating such tests, the FDA can promote the safety and efficacy of such tests by facilitating . . .
  - Clarification of their indication(s) for use and intended use population(s) – i.e., who should be tested, when and why?
  - Improved transparency and consistency in the description of "critical" performance characteristics (e.g., accuracy, precision, etc) established during initial test validation (and during subsequent modifications) to allow "apples to apples" comparisons for "consumers" (e.g., patients, providers, payers, etc.)
  - Appropriate and understandable reporting of test results, including limitations, to these "consumers"

Please note that the opinions expressed herein are my own.

Thank you.

Questions and comments are welcome.

girish.putcha@palmettogba.com

MolDX®

Please note that the opinions expressed herein are my own.

Eric Konnick

Association for Molecular Pathology

Kimberly Martin

Natera

natera™
Conceive. Deliver.

Patient and Medical Professional Perspectives on the Return of Genetic Test Results Workshop

"Doctor, does my baby have Down syndrome?"

March 2, 2016

Kimberly Martin MD, FABOG, FABMG

Senior Medical Director for Women's Health, Natera

natera™
Conceive. Deliver.

Best Practices for Reporting cfDNA Results

Pre-Test Counseling

Essential Report Components

- Easy to read & understand
- Accurate measurement & reporting of fetal fraction essential quality metric
- Screening test, NOT diagnostic
- High risk results require genetic counseling & diagnostic testing before irreversible pregnancy decisions are made

panorama™
prenatal screen

ABOUT THIS SCREEN: Panorama™ is a screening test, not diagnostic. It evaluates genetic information in the maternal blood, which is a mixture of maternal and placental DNA, to determine the chance for specific chromosome abnormalities. The test does NOT tell with certainty if a fetus is affected, and only tests for the conditions ordered by the healthcare provider. A low risk result does not guarantee an unaffected fetus.

TEST SELECTED: Sex of Fetus, Triploidy

Positive Predictive Values[4]

T21: 91%

T18: 93%

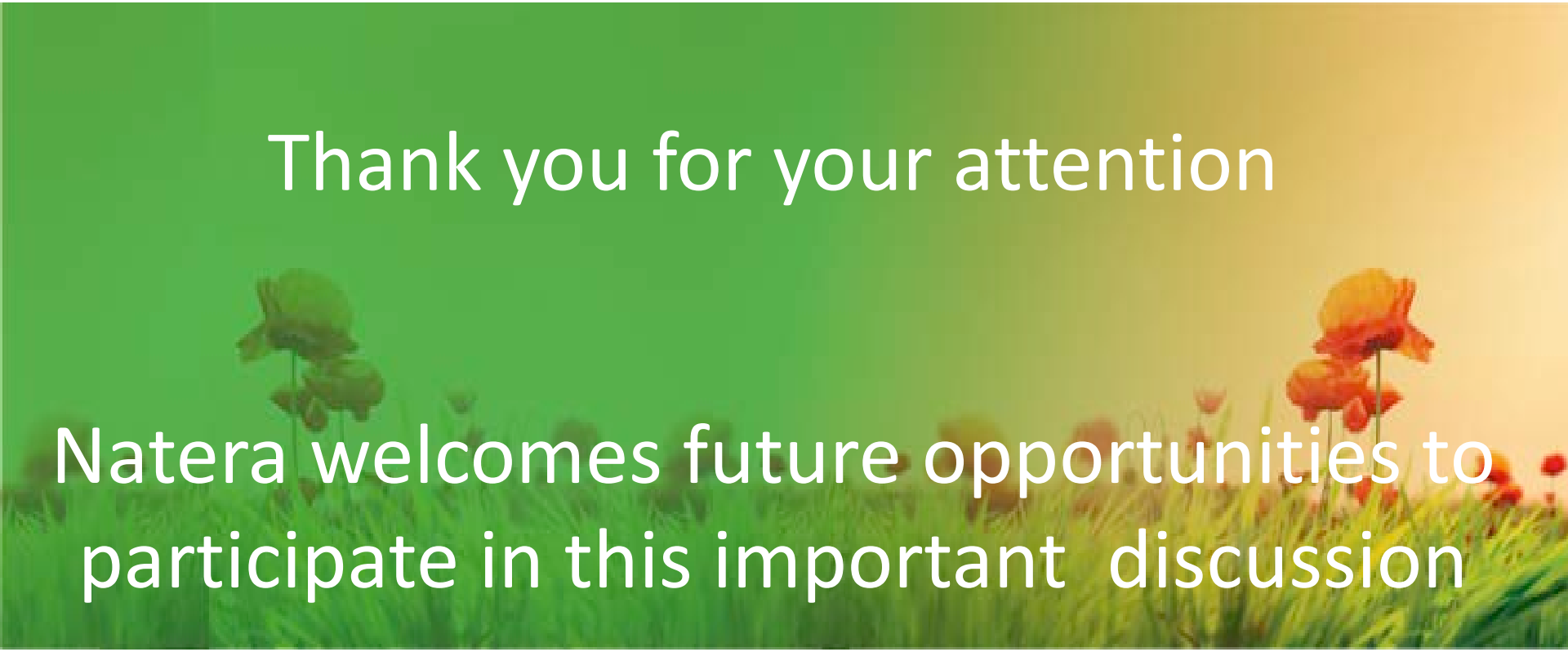
T13: 38%

MX: 50%

Positive Predictive Value (PPV) is the likelihood that diagnostic testing will confirm a High Risk result. PPV provided is NOT personalized for this patient, but calculated from a published study of 17,885 women. PPV for an individual specimen will vary based on prior risk.

natera™

Conceive. Deliver.



Matthew Rutledge

MD Labs

Making Pharmacogenetics Clinically Actionable

The Direct-to-Pharmacist Model

Copyright MD Labs 2016

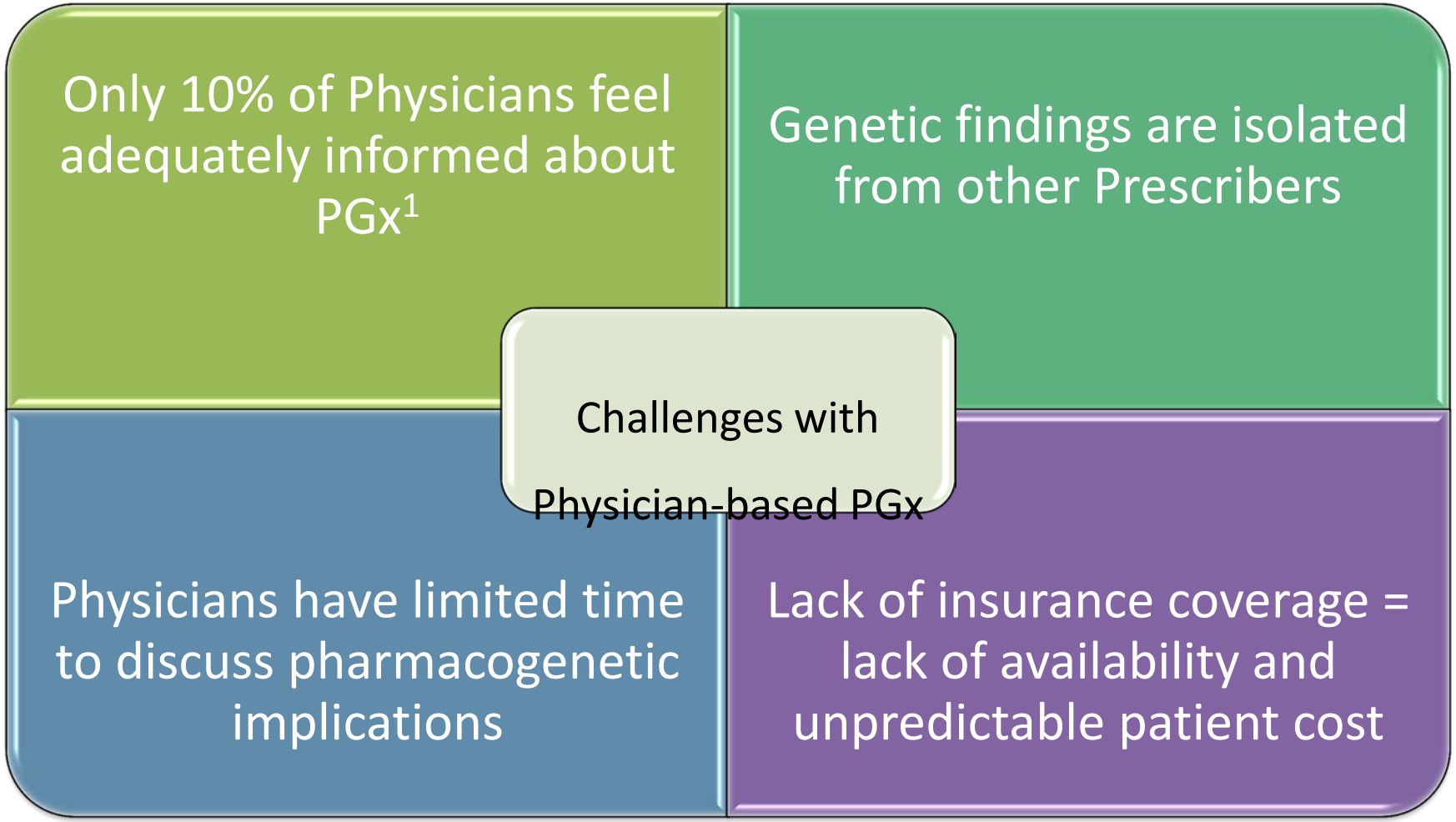
The Promise of Pharmacogenetics

Using Genetics to Optimize Medication Therapy

- Quickly identify right medication and dosage
- Avoid medications with harmful side effects, and reduce serious and deadly ADR's
- Address current and future Rx needs
- Reduce cost of ineffective medications

Copyright MD Labs 2016

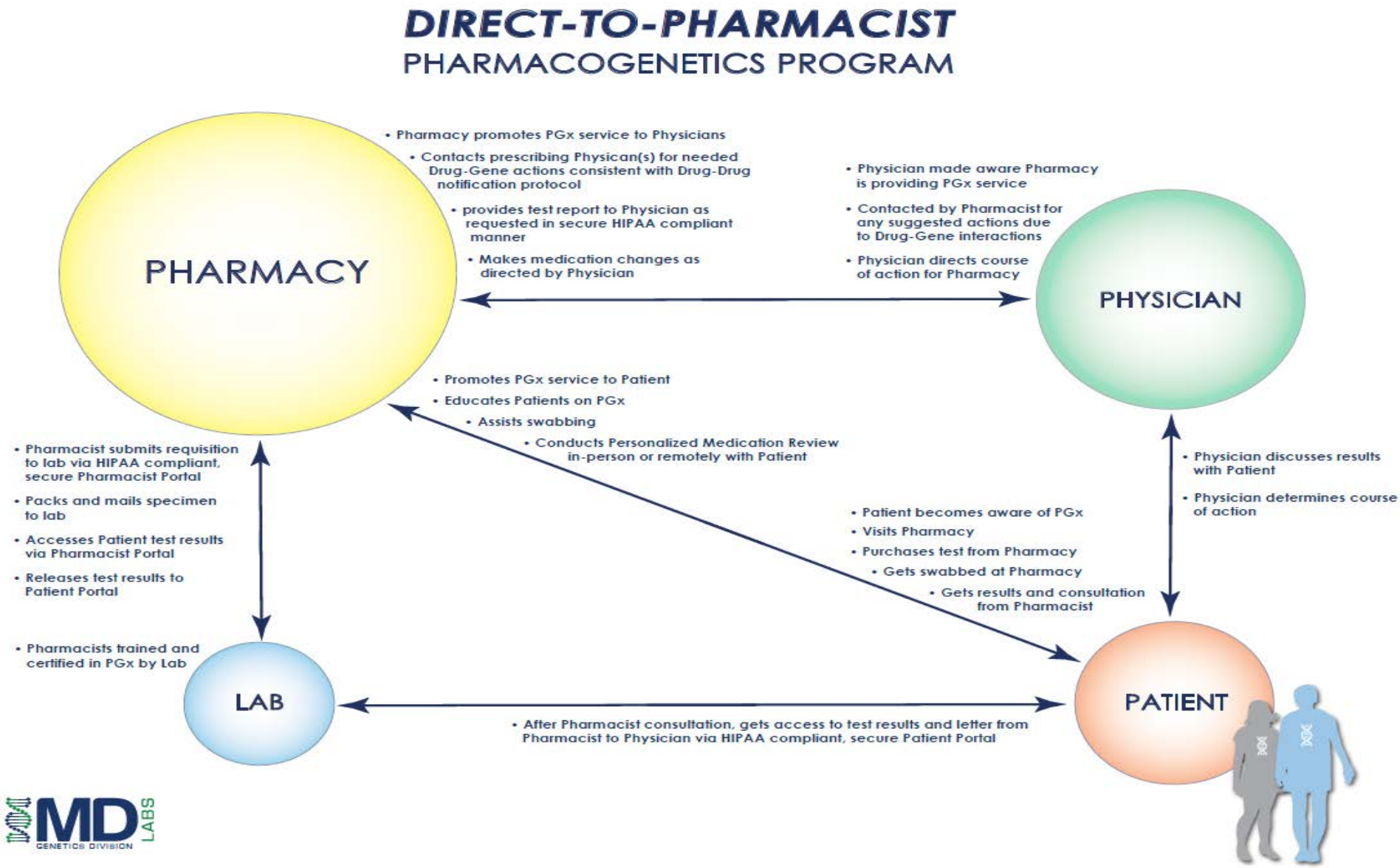
Current Challenges in the Clinical Utility of Pharmacogenetics



[1]Stanek, et al., CPT (2012)

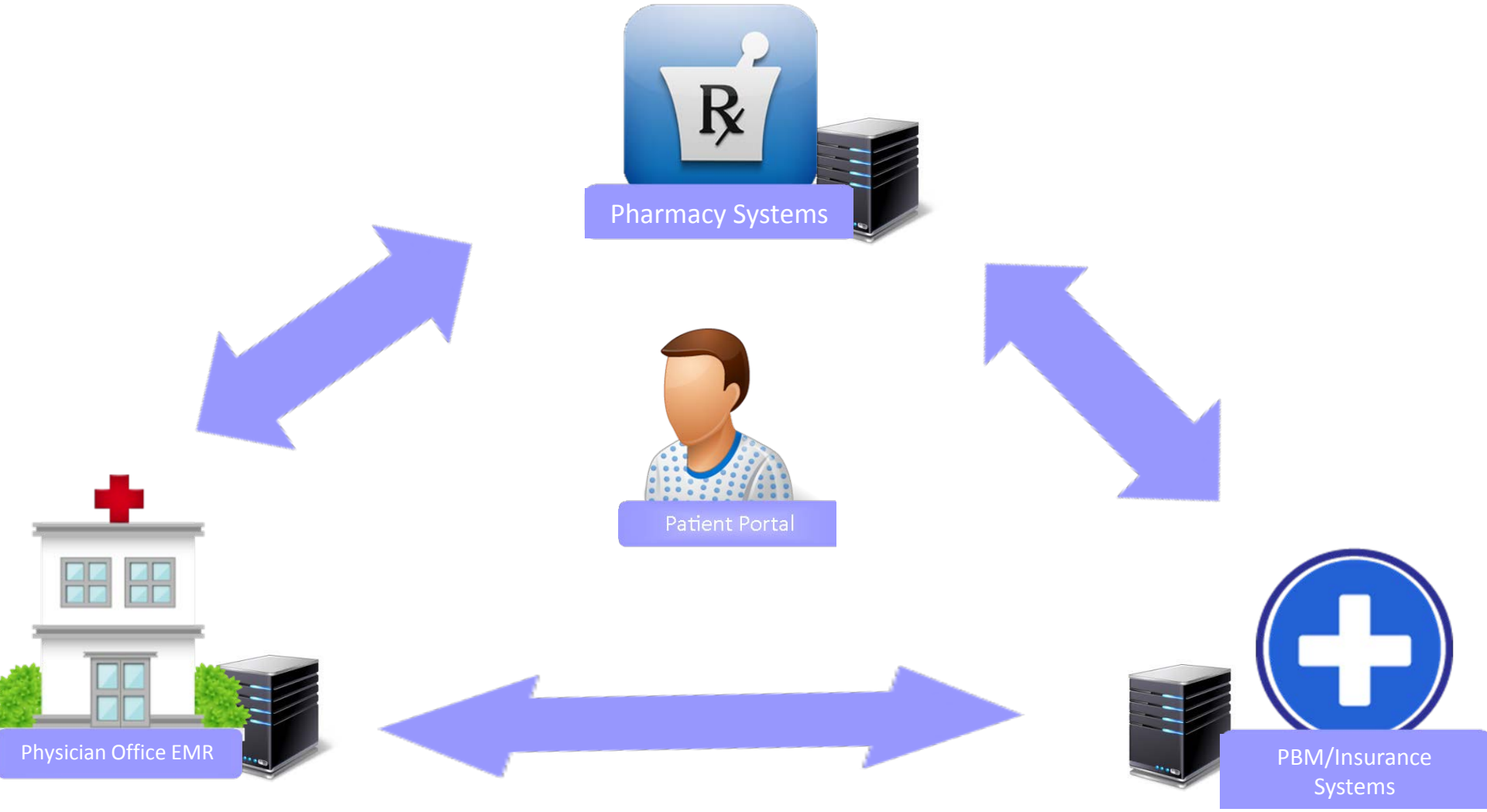
Copyright MD Labs 2016

Direct-to-Pharmacist



Copyright MD Labs 2016

Data Integration



Appendix

Copyright MD Labs 2016

PHARMACISTS

- Currently receive PGx training in school
- Currently are experts in Drug-Drug interaction and recommendations to prescribing physician. It is a natural they will be experts on Drug-Gene interaction
- Currently are curators of all patient medications (from each specialist provider)
- PGx is already part of Medication Therapy Management (MTM) process
- With PGx, medication warnings will pop-up on the Pharmacy terminal just like allergies do now to warn of genetic contraindications

Copyright MD Labs 2016

Pharmacy as the Solution

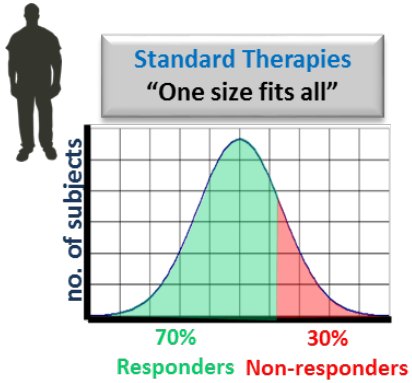
- Trained Pharmacists Conduct a Personalized Medication Review with Patients Prior to Results Being Released
- Trained Pharmacists Relay Recommendations to All Prescribing Providers Electronically
- Pharmacy Curates Patient Findings Electronically for the Life of the Patient, Updating Findings as New Research Comes To Light
- EMR Physician Office and Hospital Systems Connect Electronically to Pharmacy Database to Share Information
- App Allows Patient to Carry PGX Data Anywhere

--PHARMACY IS THE KEY

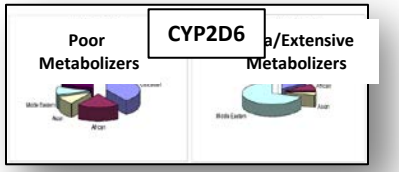
Copyright MD Labs 2016

Precision Medicine: Pharmacogenetics

Opportunity → **Knowledge** → **Solution**



DATA



CPIC™
Clinical Pharmacogenetics Implementation Consortium

PHARMACY!

Optimized Therapy

Safer Medications

CPIC Published Clinical Guidelines

Genomic Translation

Trained Specialists (PharmD's) Providing Drug-Drug and Drug-Gene Recommendations

Pharmacist-Managed Clinical Care

Copyright MD Labs 2016

Amina Abubakar

RX Clinic Pharmacy

Andy Faucett

Geisinger Health System

Geisinger – Genetic Tests - Patient Engagement and Data Sharing

Andy Faucett, MS, LGC – wafaucett@geisinger.edu

mycode

ClinGen
Clinical Genome Resource

GenomeConnect
The ClinGen Patient Portal

ClinVar

ClinVar aggregates information about genomic variation and its relationship to human health.

Geisinger

65

Sara Hart Weir

National Down Syndrome Society

national down syndrome society

ndss

- A comprehensive overview of Down syndrome written especially for parents

- This 44-page booklet includes sections on:
  - getting a healthy start
  - early intervention therapies
  - how to find support
  - caring for your family
  - what the future holds for your child
  - health care guidelines

- Last year, nearly **6,000** guides were sent to new and expectant parents in all **50 states**

- Printed copies are in available in English and Spanish

- Web-based versions: Arabic, Simplified Chinese, Russian, Vietnamese

State Down Syndrome Information Laws

•*Issue:* patients receiving prenatal or postnatal diagnosis of DS are routinely being given inaccurate, outdated information about DS by their health care providers.

- This problem was partially addressed at the federal level in the bipartisan *Prenatally and Postnatally Diagnosed Conditions Awareness Act (S. 1810, 110th)* introduced by Senator Sam Brownback and the late Senator Ted Kennedy introduced into the U.S. Senate in 2007.
- The act was intended to "increase the provision of scientifically sound information and support services to patients receiving a positive diagnostic test for Down syndrome, or other prenatally or postnatally diagnosed conditions."
- The act was passed by the Congress and signed into law by President George W. Bush on October 8, 2008.
- Unfortunately, the bill was never funded.
- In the absence of funding for the Kennedy-Brownback bill, advocates in various states have taken up this issue with their state legislatures

•*Solution:* pass legislation requiring State Dept. of Health and health care providers to distribute "up-to-date, evidence-based, written information about DS that has been reviewed by medical experts and DS organizations."

•Example: NDSS new & expectant parent guide, *A Promising Future Together*

•*Widespread State Effort*

- Bills have already passed in the following states: DE*, FL, IL*, KY, LA, MA*, MD*, ME*, MN, OH*, MO, PA, TX, SD, VA (**We recommend using the language of these bills only.)*
- States where advocates are mobilizing to bring legislation: CA, MI, WI
  - NDSS works with advocates and legislators using its Pro-Information Bill Toolkit

Sara Hart Weir, MS

President

National Down Syndrome Society

666 Broadway, 8th Floor

New York, NY 10012

(202) 680-8867

sweir@ndss.org

Tracy Trotter

American Academy of Pediatrics

Cathy Petti

Ancestry

A Universal Need for Education

- Genetic and genomic technologies are being integrated into individual and public health at an accelerated pace
  - The US ranks 27th in science based on test scores amongst 15-year-olds
  - Approximately 50% of adults are not familiar with genetic science
  - There are ~1 billion physician office visits per year
    - Less than 0.3% of healthcare professionals have special expertise in genetics
  - 50% of consumers are concerned about their physician's ability to interpret genetic test results

Benefits of Active, Individualized Learning

Via Accessible, On-Demand Genetic Testing

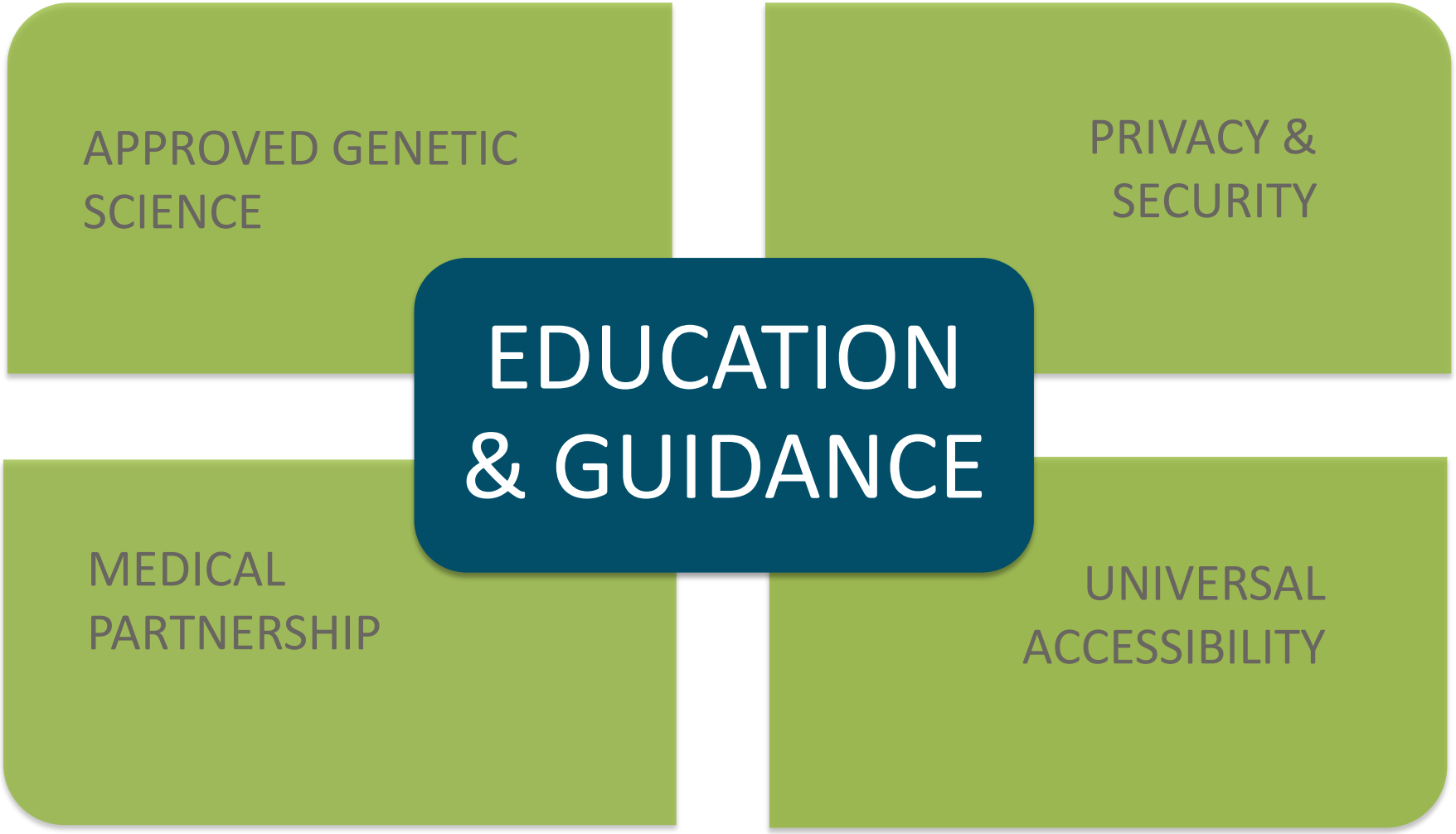
ancestry

Public health would be improved if patients had individual access to genetic tests for discussion with their physicians

…when done responsibly

ancestry

The Responsible Provider



Scott Roberts

University of Michigan School of Public Health

Andrew Sperling

National Alliance on Mental Illness

Mark Sobel

American Society for Investigative Pathology

COMMENTS TO FDA PUBLIC WORKSHOP

Patient and Medical Professional Perspectives on the Return of Genetic Test Results

March 2, 2016

The Pathology Perspective: Return of Genetic Test Results and Interpretations in the Research Setting

Mark E. Sobel MD, PhD

Executive Officer

American Society for Investigative Pathology

mesobel@asip.org

Core Principles

- **Research participants, when receiving their laboratory results, should have confidence in both the results and their interpretation.**
  - **Best Practice: Laboratory results returned to research participants should only come from CLIA-certified laboratories. Recontact to get additional samples should be allowed and not considered, in and of itself, a returnable finding.**
  - **Variance from Best Practice: Should require review by governing IRB.**

Core Principles

- **Research participants deserve the respect of knowing in advance whether and what genetic test results will be returned to them; and, if results are to be returned, the timing and procedure for receiving the results.**
- **Release of individual laboratory results should occur within the same ethical framework developed for the release of other clinical data/observations gathered during a research study.**
  - **Best practice: Inform research participants in advance whether test results will be made available and what the process is for receiving results. Both should be stated clearly in the consent.**
  - **Best practice: Research proposals should proactively address contingencies for findings that may have implications for clinical care.**
  - **Best practice: Inform research participants in advance and as part of the consent process how unanticipated incidental findings will be handled.**

Core Principles

- **Since the primary goal of scientific research is to advance generalizable knowledge, researchers should design and conduct the best possible scientific research within existing ethical guidelines.**
  - **Best Practice: The primary goal of research is <u>not</u> to return individual results to research participants. Where appropriate, researchers may return results provided that:**
    - **Patient safety receives the highest consideration – only VALID (analytical validity, test validity, clinical validity) test results should be returned**
    - **The integrity of the research study is not jeopardized**

Core Principles

- **No hard and fast policy works in all situations. Researchers should seek expert advice when faced with difficult issues.**
  - **Best Practice: The governing IRB should work with the researcher to address challenging issues and determine the appropriate course of action:**
    - **Unanticipated/incidental findings with potential clinical care implications**
    - **Return of results from a non-CLIA certified laboratory**

Core Principles

- **Research test results should be maintained separately from the medical record unless:**
  - **testing was conducted in a CLIA-certified laboratory, and**
  - **the informed consent process included this option.**

Core Principles

- **Policies related to Return of Genetic Results in the Research Setting must account for :**
  - **patient safety,**
  - **safeguard the integrity of the research study,**
  - **decreased scientific research funding,**
  - **administrative burden,**
  - **cost implications, and**
  - **the need to ensure research rigor and reproducibility**

Contact Information

Mark E. Sobel, MD, PhD

Executive Officer

American Society for Investigative Pathology

9650 Rockville Pike

Bethesda, MD 20814

301-634-7130

mesobel@asip.org

http://www.asip.org

Rick Kelly

Equipay

Shannon Curtis

American Medical Association

Judith Nwachukwu

Veteran Affairs Medical Center

Sally Okun

PatientsLikeMe

PUBLIC COMMENT

CLOSING REMARKS

Jeffrey Shuren, JD, MD
Director, Center for Devices and Radiological Health
Food and Drug Administration

Docket No. FDA-2015-N-4809